OFFICE (MODIFIED)

X-11506

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)

10/088002

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/21974	09/18/2000 (09.18.00)	09/27/1999 (09.27.99)

TITLE OF INVENTION: PROCESS FOR PREPARING BENZOIC ACIDS

APPLICANT(S) FOR DO/EO/US: Wayne Douglas Luke

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [X] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [X] A copy of the International Preliminary Examination Report (IPER), including any annexes, and, if not in English, an English language translation of the annexes to the IPER under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

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17. [X] The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$1040.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$750.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**

International preliminary examination fee paid to USPTO (37 CRF 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than __20 __30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	14 - 20=		**X $18.00**	$	
Independent claims	1 - 3=		**X $84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $280.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 890.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 890.00	
Processing fee of **$130.00** for furnishing English translation later than __ 20 __30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 890.00	
				Amount to be refunded	$
				charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 05-0840 in the amount of $890.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 05-0840. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
ELI LILLY AND COMPANY
PATENT DIVISION/XXX
LILLY CORPORATE CENTER

3-11-02
Date

44,712
REGISTRATION NUMBER

Francis O. Ginah
SIGNATURE

Francis O. Ginah
NAME

(317) 276-9477
TELEPHONE NUMBER

25885
25885
PATENT TRADEMARK OFFICE

"Express Mail" mailing label number EL832892385US

Date of Deposit MAR. 11, 2002

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Arlington, VA 22202.

QUEEN THOMAS
Printed Name

Signature

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Wayne Douglas Luke)
)
For : PROCESS FOR PREPARING)
BENZOIC ACIDS)
)
Docket No. : X-11506)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Arlington, VA 22202
Sir:

In the Specification

In the application, Claims 1 to 14 are pending. Applicants hereby make the following preliminary amendments.

In the Claims

Applicants herewith amend Claims 5 and 14 and further add new Claim 15.

5. (amended) A process according to Claim [1]4 wherein said C_1-C_6 alkyl acetate solvent is amyl acetate.

14. (amended) A process according to Claim 1 [or 13] wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

Docket No. X-11506

15. (new) A process according to Claim 13 wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

Remarks

Applicants thank the Examiner in advance for entering these preliminary amendments. Applicants have enclosed an amended claim set and a current claim set for your reference.

Respectfully submitted,

Francis O. Ginah

Francis O. Ginah
Attorney for Applicants
Registration No. 44,712
Phone: 317-276-9477

Eli Lilly and Company
Patent Division/FOG
Lilly Corporate Center
Indianapolis, Indiana 46285

21, February 2002

Amended Claim Set (02/21/02)

5. (amended) A process according to Claim [1]4 wherein said C_1-C_6 alkyl acetate solvent is amyl acetate.

14. (amended) A process according to Claim 1 [or 13] wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

15. (new) A process according to Claim 13 wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

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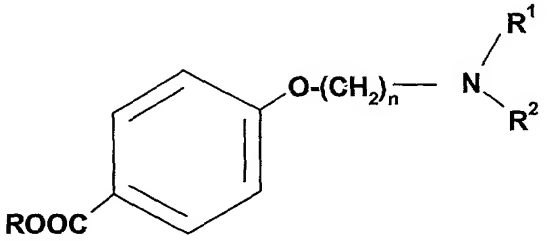
JC13 Rec'd PCT/PTO 11 MAR 2002

Current Claim Set (02/21/02)

1. A process for preparing a compound of formula I



I

wherein;

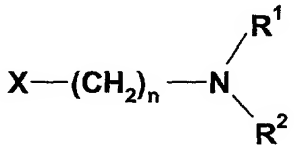
R is C_1-C_6 alkyl;

R^1 and R^2 each are independently C_1-C_4 alkyl, or combine together with the nitrogen atom to which R^1 and R^2 are attached, to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, or 1-hexamethyleneimino; and

n is 2 or 3;

or a pharmaceutically acceptable salt thereof, which comprises the step of:

reacting a haloalkyl amine of formula III

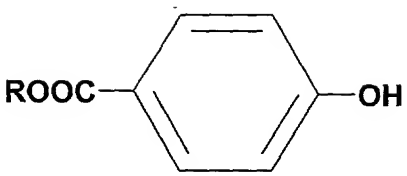


III

wherein;

X is a halogen; and

R^1, R^2, and n are as defined above, with a compound of formula IV



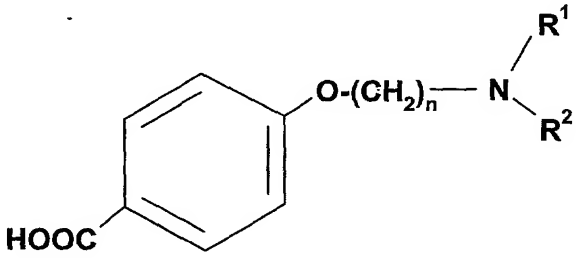
IV

wherein R is C_1-C_6 alkyl, in the presence of a hydrated inorganic base and an appropriate solvent.

2. The process according to Claim 1 further comprising the steps of:

a) extracting the reaction product of Claim 1 with an aqueous acid; and optionally

b) cleaving the ester of the reaction product from step a) to form an acid compound of formula Ia



Ia

3. A process according to Claim 1 wherein the hydrated inorganic base is selected from the group consisting of potassium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, calcium carbonate.

4. A process according to Claim 1 wherein the solvent is a C_1-C_6 alkyl acetate solvent selected from the group consisting of amyl acetate, isopropyl acetate, isobutyl acetate and ethyl acetate.

5. A process according to Claim 4 wherein said C_1-C_6 alkyl acetate solvent is amyl acetate.

6. A process according to Claim 1 wherein said hydrated inorganic base is a carbonate or bicarbonate salt.

7. A process according to Claim 6 wherein said carbonate salt is potassium carbonate hydrated with 1-20% water.

8. A process according to Claim 7 wherein said hydrated potassium carbonate is achieved by adding bulk water.

9. A process according to Claim 7 wherein said hydrated potassium carbonate is achieved by water of hydration.

10. A process according to Claim 7 wherein said carbonate salt is potassium carbonate sesquihydrate.

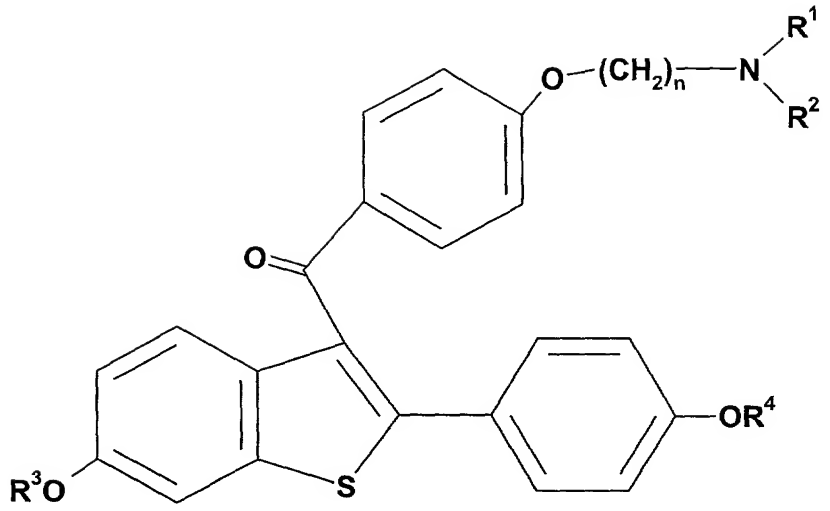
11. A process according to Claim 1 wherein R^1 and R^2 combine together with the nitrogen atom to which R^1 and R^2 are attached, to form piperidinyl; and

n is 2;

or a pharmaceutically acceptable salt thereof.

12. A process according to Claim 2 wherein said aqueous acid is hydrochloric acid.

13. A process according to Claim 2 for preparing compounds of formula II



II

wherein;

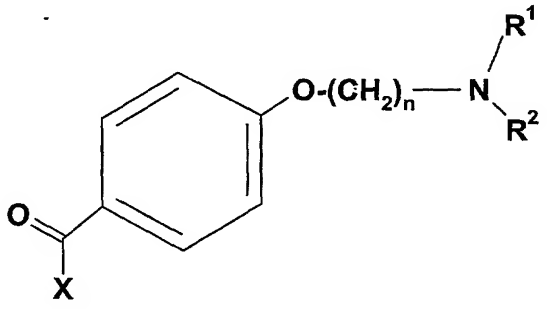
R^3 and R^4 are independently hydrogen or a hydroxy protecting group; and

R^1, R^2 and n are as defined above;

or a pharmaceutically acceptable salt thereof,

comprising the steps of:

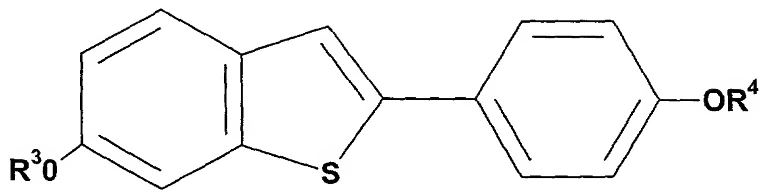
a) reacting a compound of formula I or Ia with an acyl halide forming agent to form a compound of formula V



V ;

wherein X is a halogen, and

b) reacting a compound of formula V with a compound of formula VI



VI

wherein R^3 and R^4 are as defined above, or a pharmaceutically acceptable salt thereof.

14. A process according to Claim 1 wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

15. A process according to Claim 13 wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

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PCT/US00/21974

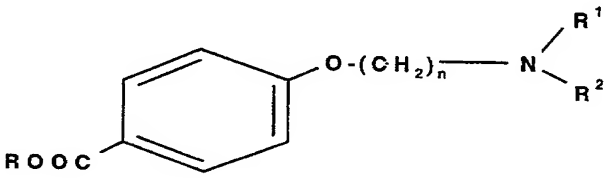
PROCESS FOR PREPARING BENZOIC ACIDS

Field of the Invention

The present invention relates to the fields of pharmaceutical and organic chemistry and provides a novel process for preparing 4[(2-piperidin-1-yl)ethoxy]benzoic acid derivative compounds.

Background of the Invention

Compounds of formula I



I

wherein;

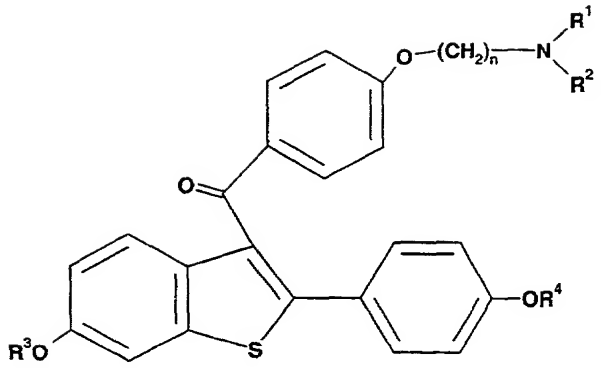
R is C_1-C_6 alkyl;

R^1 and R^2 each are independently C_1-C_4 alkyl, or combine together with the nitrogen atom to which R^1 and R^2

n is 2 or 3;

or acid salt thereof;

are important intermediates in the manufacture of compounds of formula II



II

wherein;

R^3 and R^4 are independently hydrogen or a hydroxy protecting group; and

R^1, R^2 and n are as defined above;

or a pharmaceutically acceptable salt thereof.

Compounds of formula II, particularly raloxifene hydrochloride, in which R^1 and R^2 combine to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, are well known in the pharmaceutical art as having activity for the treatment or prevention of certain disease states including, for example, osteoporosis.

Typically, compounds of formula I are prepared by reacting, for example, β-chloroethylpiperidine hydrochloride and ethyl 4-hydroxybenzoate in methyl ethyl ketone, in the presence of potassium carbonate (see, U.S. Pat. No. 4,418,068). An improved process for preparing compounds of formula I was disclosed in U.S. Patent No. 5,631,369, the contents of which are incorporated herein

by reference. The disclosures of both reference patents teach the use of anhydrous powdered potassium carbonate as the preferred base for enhancing the rate of the reaction, implying that the particle size of anhydrous potassium carbonate is crucial to the alkylation reaction.

Powdered potassium carbonate is relatively more expensive than granular hydrated potassium carbonate, and a controlled atmosphere may be required to maintain the anhydrous nature of powdered potassium carbonate. These factors add to the overall cost of manufacture of compounds of formula I and II.

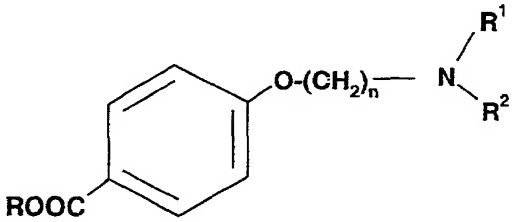
Furthermore, the use of anhydrous potassium carbonate on a manufacturing scale results in a heterogenous mixture, thus limiting the ability to effectively agitate the mixture. This in turn makes it difficult to perform the reaction at a higher concentration, resulting ultimately in a lower throughput.

A more efficient, more robust and less costly process for preparing compounds of formula I and ultimately compounds of formula II is needed. Such a process would ideally obviate the use of powdered anhydrous potassium carbonate. Such a process would also result in a homogenous reaction mixture which increases reaction concentration and hence throughput. Such a process would be a significant and desirable advancement

over the current state of the art. The present invention provides such a process.

Summary of the Invention

The present invention provides a novel process for preparing compounds of formula I



I

wherein;

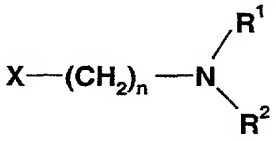
R is C_1-C_6 alkyl;

R^1 and R^2 each are independently C_1-C_4 alkyl, or combine together with the nitrogen atom to which R^1 and R^2 are attached, to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, or 1-hexamethyleneimino; and

n is 2 or 3;

or an acid salt thereof, which comprises:

reacting a haloalkyl amine of formula III

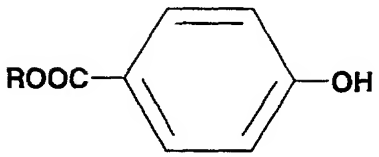


III

wherein;

X is a halogen; and

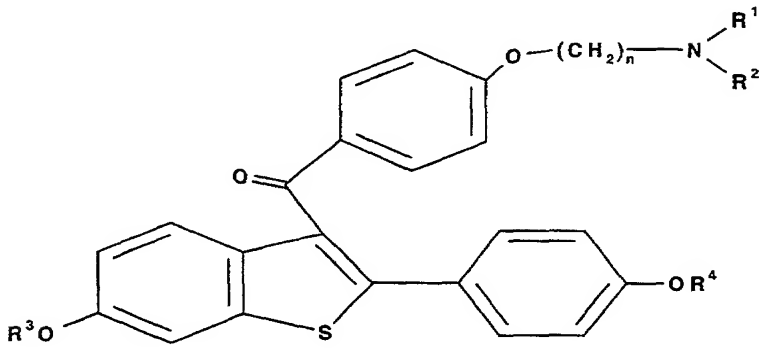
R^1, R^2, and n are as defined above, with a compound of formula IV:



IV

wherein R is C_1-C_6 alkyl, in the presence of a hydrated inorganic base, in an appropriate solvent.

The present invention further provides a process for preparing compounds of formula II



II

wherein;

R^1, R^2 and n, are as defined above and;

R^3 and R^4 are each independently hydrogen or a hydroxy protecting group; and

n is 2 or 3;

or a pharmaceutically acceptable salt thereof, from compounds of formula I.

Detailed Description of the Invention

General terms used in the description of chemical formulae herein bear their usual meanings. For example, the term "C_1-C_4 alkyl" refers to straight or branched chains of 1 to 4 carbon atoms including, methyl, ethyl, propyl, isopropyl, butyl, n-butyl, and isobutyl; and the term "C_1-C_6 alkyl" encompasses the groups included in the definition of "C_1-C_4 alkyl" in addition to groups such as pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "halo" or "halogen" includes bromo, chloro, fluoro, and iodo.

The term "appropriate solvent" as used herein refers to a C_1-C_6 alkyl acetate possessing the desired boiling point for the particular reaction substrate, and possessing an appropriate miscibility with an aqueous phase for the substrate of the reaction.

The terms "appropriate aqueous acid" or "appropriate acid" as used herein refer to any one of the inorganic or organic acids capable of protonating a basic group such as an amino group or a carboxylate anion to form the corresponding acid addition salt or acid, without effecting deleterious manipulations of the molecule.

Examples include but are not limited to aqueous hydrochloric acid, anhydrous hydrogen chloride, dilute phosphoric acid, dilute sulfuric acid, acetic acid and the like.

The term "acid salt" as used herein denote non-covalently bonded, addition compounds formed by the reaction of an organic or inorganic acid which is water soluble, preferably an inorganic acid with a basic molecule i.e., a molecule containing typically an amino group or other nitrogen atom containing group, for example, a compound of formula I.

The term "hydrated inorganic base" as used herein refers to non-anhydrous inorganic base, for example, sodium carbonate containing from 1 to 20% water of hydration or up to the limit of hydration for the particular base. The water content (hence the hydration) can be attained by (1) addition of water as a bulk solvent or (2) introduced with potassium carbonate as water of hydration of the potassium carbonate. Hydrated potassium carbonate can be obtained commercially as potassium carbonate sesquihydrate.

The terms "hydroxy protecting group" and "-OH protecting group" as used herein are synonymous, and bear the commonly understood meaning and refer particularly, to a group used to replace the hydrogen atom of a hydroxy group for the purposes of avoiding reaction at the hydroxy group, providing bulk or other generally understood purposes.

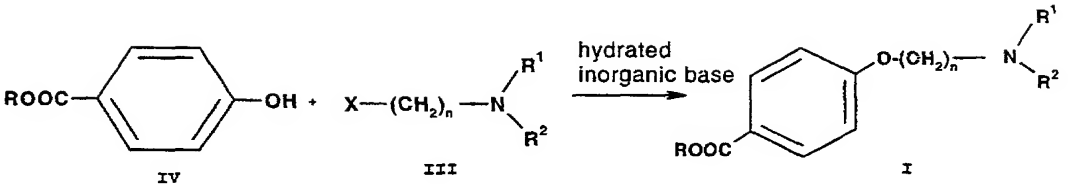
In formula II compounds, the R^3 and R^4 hydroxy protecting groups, when R^3 and R^4 are not hydrogen, denote groups which generally are not found in the final therapeutically active compounds, but which are intentionally introduced during a portion of the synthetic process to protect a group which otherwise might react in

the course of chemical manipulations, and is then removed at a later stage of the synthesis. Since compounds bearing such protecting groups are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity), their precise structure is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, *Protective Groups in Organic Chemistry*, Plenum Press (London and New York, 1973); Green, T.W., *Protective Groups in Organic Synthesis*, Wiley (New York, 1981); and *The Peptides*, Vol. I, Schrooder and Lubke, Academic Press (London and New York, 1965). Representative hydroxy protecting groups include, for example, -C_1-C_4 alkyl, -CO-(C_1-C_6 alkyl), -SO_2-(C_4-C_6 alkyl), and -CO-Ar in which Ar is optionally substituted phenyl.

The term "substituted phenyl" refers to a phenyl group having one or more substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_5 alkoxy, hydroxy, nitro, chloro, fluoro, and tri(chloro or fluoro) methyl. The term "C_1-C_5 alkoxy" represents a C_1-C_5 alkyl group attached through an oxygen bridge such as, for example, methoxy, ethoxy, n-propoxy, isopropoxy, and the like. Preferred R^3 and R^4 hydroxy protecting groups are C_1-C_4 alkyl, particularly methyl.

The present invention provides a process for preparing a compound of formula I which is illustrated in Scheme 1 below:

Scheme 1



where X, R^1, R^1 and R^2 are defined above.

In the present novel process, an amount of a haloalkyl amine of formula III is reacted with about 1 mole equivalent of a 4-hydroxybenzoate of formula IV and a hydrated inorganic base, in the presence of an appropriate solvent. Typically from about 1 to 3 molar equivalents, preferably from about 1 to 1.5 molar equivalents and most preferably about 1.05 molar equivalent of haloalkyl amine of formula III is utilized. Similarly from about 1 to 3 molar equivalents, preferably from about 1 to 1.5 molar equivalents and most preferably 1.05 molar equivalent of base is utilized. A preferred formula III compound is that in which R^1 and R^2 combine to form piperidinyl, n is 2, and X is chloro, while a preferred formula IV compound is that in which R is methyl.

A preferred solvent is a C_1-C_6 alkyl acetate solvent including those in which the alkyl moiety of such solvent is a straight or branched chain alkyl moiety having one to six carbon atoms. Preferred alkyl acetate solvents include, for example, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, amyl acetate, isoamyl acetate, and the like. A most preferred C_1-C_6 alkyl acetate solvent is amyl acetate.

In addition to an alkyl acetate solvent, the present process, as well as the processes described below, is run in the presence of an appropriate hydrated inorganic base. A hydrated inorganic base such as a carbonate or bicarbonate base, is preferred. Of these, granular potassium carbonate containing from about 1-20% of water is preferred. Granular potassium carbonate with from about 3-5% water content is the most efficient for enhancing the rate of completion of the reaction and hence is most preferred for the practice of the invention.

Furthermore, it is preferred to maintain the alkylation reaction mixture under an inert atmosphere, such as, for example, argon, or, particularly, nitrogen.

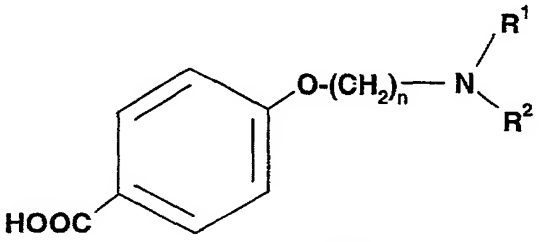
The present reaction may be run at a temperature from about 80°C to the reflux temperature of the solvent. A preferred temperature range is from about 100°C to about 150°C, while a range from about 118°C to about 125°C is especially preferred.

The length of time for this reaction is that amount necessary for the reaction to substantially occur. Typically, this reaction takes from about 2 to 24 hours. The optimal time can be determined by monitoring the progress of the reaction via conventional chromatographic techniques. A preferred reaction time is from 2 to 6 hours. A particularly preferred reaction time is from 4.5 to 5.5 hours. A most preferred reaction time is from 4 to 4.5 hours.

Upon completion of this reaction, the alkylation mixture is cooled, to between about 30°C and about 70°C, and washed with water to dissolve the added basic salt. An appropriate aqueous acid is then added to the mixture to extract the compound of formula I.

Preferably, aqueous hydrochloric acid is used for the extraction process, forming a hydrochloride salt of the formula I compound. Other aqueous acids such as, for example, sulfuric acid, phosphoric acid, acetic acid and the like, may be used, and the corresponding formula I acid salt is provided. One of skill in the art is aware that the compound of formula I may optionally be isolated as the free base by methods known in the art including but not limited to chromatography, distillation and or crystallization. Preferably, the acid salt of the formula I compound may be utilized *in- situ* without isolation.

Optionally, the aryl or alkyl ester of the desired formula I compound is cleaved via standard procedures, providing a compound of formula Ia



Ia

wherein;

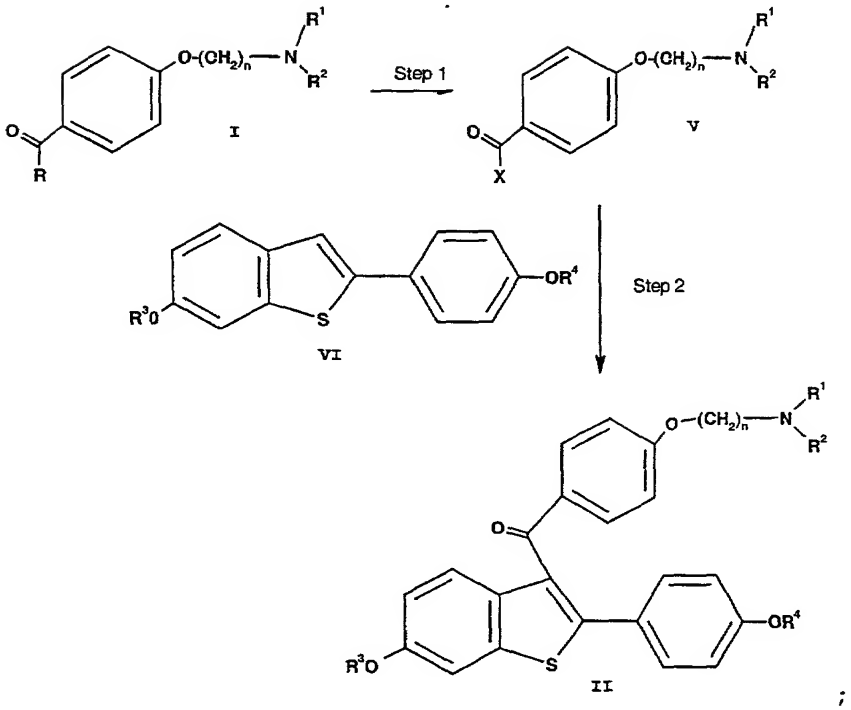
R1, R2, and n are as defined above.

Typically, the formula I acid compound is heated to a temperature in the range from about 80°C to about 150°C, preferably from about 95°C to about 100°C. At the preferred temperature range, an acceptable level of formula Ia compound is produced in about 4 hours. Continued heating for up to 24 hours will not affect either quality or yield. Optionally, while applying heat in the above-stated temperature range, the ester cleaving may be accelerated by distilling and removing the alcohol formed via acid hydrolysis.

Isolation and purification of the acid compound, formula Ia, is accomplished using procedures well known to one of ordinary skill in the art (See also U.S. Patent No. 5,631,369). Generally, the resulting mixture from the ester cleavage step is cooled to a temperature range from about -5°C to about 20°C. Although the product will crystallize or precipitate out of solution at this range, the optimum temperature range is from about 0°C to about 5°C. The desired formula Ia compound is then isolated by filtration or other techniques known to practitioners of the art.

Compounds of formula I or derivatives thereof, can be converted to the compounds of formula II as illustrated in scheme 2 below:

Scheme 2



;

wherein X is a halogen, preferably bromine or chlorine; and R, R^1, R^2, R^3, and R^4 are as defined above.

In general, a compound of formula I or its derivative such as the amide, formyl or acid derivates are converted to the acid halide compound of formula V, preferably an acid chloride or acid bromide, by methods well known to one skilled in the art. General reference texts for the formation of acid chlorides (acyl halides) include for example, March, J. *Advanced Organic Chemistry*, John Wiley and Sons, New York, N.Y., 1985, and Larock, R.C. *Comprehensive organic transformations*, (1989), VCH Publishers Inc. New York, NY. A preferred procedure for acyl halide formation (step 1) involves reacting the acid compound Ia, with an acyl halide

forming reagent to provide a compound of formula V, in a solvent such as dichloromethane, 1,2-dichloroethane, toluene or tetrahydrofuran. Typical acyl halide forming reagents include but are not limited to phospgene, thionyl chloride, oxalyl chloride, phosphorus trichloride, triphenylphosphine dibromide and acids such as hydrochloric, and hydrogen fluoride. Preferred acyl halide forming agents for the practice of this invention include oxalyl chloride, anhydrous hydrogen chloride, thionyl chloride. Most preferred is thionyl chloride.

In step 2, the acyl halide compound of formula V may be acylated with a compound of formula VI to provide a compound of formula II. Compounds of formula VI and procedures for the acylation step are known in the art and are also described for example, by Peters in U.S. Pat. No. 4,380,635, and in Jones, *et al.*, in U.S. Pat. Nos. 4,133,814 and 4,418,068, each of which is herein incorporated by reference. A preferred formula I compound for the present acylation reaction is that in which R^1 and R^2 are combined together with the nitrogen atom to which R^1 and R^2 are attached, to form piperidinyl and n is 2.

One skilled in the art is aware that particular steps of the process of this invention may be inverted or omitted without adverse effect on the practice of the invention. Furthermore certain steps such as formation of pharmaceutically acceptable salts, deprotection and/or exchange of protecting groups may be performed at different points and such acts may be advantageous depending on the particular starting material or derivatives thereof employed.

Reagents and all parameters necessary to carry out the acylation, the optional deprotection, an optional salt formation step within scheme 2, and isolation and purification of formula II compounds are described in the afore-incorporated United States patents. Thus, pharmaceutically active compounds of formula II, including their acid addition salts, are prepared via the instant process of the present invention.

Examples

The following examples are provided for the purpose of illustrating the present invention and are not intended to be limiting upon the scope of the invention.

Example 1

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

To a 2000 gallon reaction tank were added: 1320L of amyl acetate, 167.42kg of methyl 4-hydroxybenzoate, 408.6kg of anhydrous potassium carbonate, and 283.5kg of β-chloroethylpiperidine hydrochloride. The mixture was heated to 120°C - 125°C for 5 hours, at which time HPLC analysis indicated complete consumption of the methyl 4-hydroxybenzoate. The tank was cooled to less than 50°C. 880L of deionized water were added to the tank. The layers were separated and the aqueous layer was discarded. In a glass-lined tank was mixed 367 liters of food grade hydrochloric acid and 184L of deionized water. The acid mixture was combined with the organic layer.

The layers were separated and the organic layer was discarded. The mixture of the intermediate ester in aqueous acid heated to reflux until HPLC suggested no further consumption of the ester (13 hours). The mixture was cooled to less than 40°C, 550 liters of acetone was added to the mixture and the mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration on a centrifuge. The wet cake was rinsed on the centrifuge with 400L of acetone. The product was dried in a rotary vacuum (double cone) dryer at less than 50°C and 25-27 inches in mercury. Yield was 91% of theoretical.

Example 2

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

A 17.57g portion of methyl 4-hydroxybenzoate and 132mL of amyl acetate were combined. To this slurry at ambient temperature, was added 29.19g of potassium carbonate sesquihydrate (particle size 96% greater than 100 mesh, 100% greater than 200 mesh) and 20.26g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 110°C – 115°C for 4.5 hours. The solution was cooled to less than 50°C and 88ml of deionized water were added. The layers were separated and the aqueous layer was discarded. To the organic phase was added 88mL of deionized water the biphasic mixture stirred for 15 minutes and the phases separated. The aqueous phase was discarded. A dilute solution of aqueous hydrochloride acid was prepared by adding 42.6g of reagent grade hydrochloric acid to 15mL of deionized water. This solution was added to the organic phase, stirred for 15

minutes and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 55mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 90.6% of theory. The potency of the product by HPLC compared to a reference standard was 99.2%.

Example 3

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

A 17.57g portion of methyl 4-hydroxybenzoate and 132mL of amyl acetate were combined. To this slurry at ambient temperature, was added 29.19g of powdered potassium carbonate (11% water by Karl Fischer particle size not less than 95% passing a 100 mesh sieve and not less than 90% passing a 200 mesh sieve) and 20.26g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 110°C - 115°C for 4.5 hours. The solution was cooled to less than 50°C and 88mL of deionized water were added. The layers were separated and the aqueous layer was discarded. To the organic phase was added 88mL of deionized water the biphasic mixture stirred for 15 minutes and the phases separated. The aqueous phase was discarded. A dilute solution of aqueous hydrochloride acid was prepared by adding 42.6g of reagent grade hydrochloric acid to 15mL of deionized water. This

solution was added to the organic phase, stirred for 15 minutes and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 55mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 93.4% of theory. The potency of the product by HPLC calibrated against a reference standard was 101.0%.

Example 4

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

A 17.57g portion of methyl 4-hydroxybenzoate and 132mL of amyl acetate were combined. To this slurry at ambient temperature, was added 29.19g of powdered potassium carbonate (11% water by Karl Fischer particle size not less than 95% passing a 100 mesh sieve and not less than 90% passing a 200 mesh sieve), 4.78g of deionized water and 20.26g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 118°C - 125°C for 4.5 hours. The solution was cooled to less than 50°C and 88mL of deionized water were added. The layers were separated and the aqueous layer was discarded. To the organic phase was added 88mL of deionized water the biphasic mixture stirred for 15 minutes and the phases separated. The aqueous phase was discarded. A dilute solution of aqueous hydrochloride acid was prepared by

adding 42.6g of reagent grade hydrochloric acid to 15mL of deionized water. This solution was added to the organic phase, stirred for 15 min and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 55mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 91.3% of theory. The potency of the product by HPLC calibrated against a reference standard was 101.0%.

Example 5

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

A 50.22g portion of methyl 4-hydroxybenzoate and 198mL of amyl acetate were combined. To this slurry at ambient temperature, was added 122.58g of powdered potassium carbonate (0.8% water by Karl Fischer particle size not less than 95% passing a 100 mesh sieve and not less than 90% passing a 200 mesh sieve), 19.61g of deionized water and 85.04g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 118°C - 125°C for 4.5 hours. The solution was cooled to less than 50°C and 132mL of deionized water were added. The layers were separated and the aqueous layer was discarded. To the organic phase was added 132mL of deionized water the biphasic mixture stirred for 15 minutes and the phases separated. The aqueous phase was discarded. A dilute

solution of aqueous hydrochloride acid was prepared by adding 127.8g of reagent grade hydrochloric acid to 45mL of deionized water. This solution was added to the organic phase, stirred for 15 minutes and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 123.7mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 93.7% of theory. The potency of the product by HPLC vs a reference standard was 100.0%.

Example 6

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

A 37.66g portion of methyl 4-hydroxybenzoate and 198mL of amyl acetate were combined. To this slurry at ambient temperature, was added 91.93g of powdered potassium carbonate (0.8% water by Karl Fischer particle size not less than 95% passing a 100 mesh sieve and not less than 90% passing a 200 mesh sieve), 14.7g of deionized water and 63.78g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 118°C - 125°C for 4.5 hours. The solution was cooled to less than 50°C and 132mL of deionized water were added. The layers were separated and the aqueous layer was discarded. To the organic phase was added 132mL of deionized water the biphasic mixture stirred for 15 minutes and the phases

separated. The aqueous phase was discarded. A dilute solution of aqueous hydrochloride acid was prepared by adding 95.85g of reagent grade hydrochloric acid to 33.75mL of deionized water. This solution was added to the organic phase, stirred for 15 minutes and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 123.7mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 93.2% of theory. The potency of the product by HPLC versus a reference standard was 100.5%.

Example 7

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

A 50.22g portion of methyl 4-hydroxybenzoate and 198mL of amyl acetate were combined. To this slurry at ambient temperature was added 122.58g of powdered potassium sesquihydrate and 85.04g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 118°C - 125°C for 4.5 hours. The solution was cooled to less than 50°C and 132mL of deionized water were added. The layers were separated and the aqueous layer was discarded. To the organic phase was added 132mL of deionized water the biphasic mixture stirred for 15 minutes and the phases separated. The aqueous phase was discarded. A dilute solution of aqueous hydrochloride

acid was prepared by adding 63.9g of reagent grade hydrochloric acid to 45mL of deionized water. This solution was added to the organic phase, stirred for 15 minutes and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 123.7mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 94.7% of theory. The potency of the product by HPLC versus a reference standard was 99.2%.

Example 8

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride Effect of water content and potassium particle size on reaction

A 25.11g portion of methyl 4-hydroxybenzoate and 198mL of amyl acetate were combined. To this slurry at ambient temperature, was added 61.29g of powdered potassium carbonate (0.8% water by Karl Fischer particle size not less than 95% passing a 100 mesh sieve and not less than 90% passing a 200 mesh sieve) and 42.52g of β-chloroethylpiperidine hydrochloride. The mixture was heated to 118°C - 125°C for 4.5 hours at which time HPLC analysis indicated complete consumption of the methyl 4-hydroxybenzoate. The solution was cooled to less than 50°C and 132mL of deionized water were added. The layers were separated and the aqueous layer was discarded. To the

organic phase was added 132mL of deionized water the biphasic mixture stirred for 15 minutes and the phases separated. The aqueous phase was discarded. A dilute solution of aqueous hydrochloride acid was prepared by adding 63.9g of reagent grade hydrochloric acid to 22.5mL of deionized water. This solution was added to the organic phase, stirred for 15 min and the phases separated. The organic phase was discarded. The aqueous phase was heated to reflux for 5 hours. After approximately 1.5 hours at reflux the desired product began to precipitate. The product slurry was cooled to less than 40°C and 123.7mL of acetone was added. The mixture was cooled to 0°C - 5°C and stirred for 1 hour. The product was collected by filtration and washed with a minimum of acetone pre-chilled to 0°C. The product was dried in a vacuum oven at ambient temperature. Yield was 90.8% of theory. The potency of the product by HPLC versus a reference standard was 100.0%.

Example 9

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

The procedure of Example 8 was followed except that the particle size of the anhydrous potassium carbonate was as follows 94.4% passing a 10 mesh sieve, 88.8% passing a 20 mesh sieve, 77.4% passing a 40 and 100 mesh sieve and no material passing a 325 mesh sieve. After the initial reaction period of 4.5 hours at 118°C - 125°C less than 15% of the methyl 4-hydroxybenzoate had been converted to methyl 4-(2-piperidinoethoxy) benzoate.

Example 10

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

The procedure of Example 8 except that 1.84g of deionized water (3% by weight of the potassium carbonate charged) was added immediately after the potassium carbonate charge. After the initial reaction period of 4.5 hours at 118°C - 125°C HPLC analysis indicated complete consumption of the methyl 4-hydroxybenzoate. Yield was 91.6% of theory. The potency of the product by HPLC versus a reference standard was 99.3%.

Example 11

Preparation of 4-(2-piperidinoethoxy) benzoic acid hydrochloride

The procedure of Example 8 except that 9.8g of deionized water (16% by weight of the potassium carbonate charged) was added immediately after the potassium carbonate charge. After the initial reaction period of 4.5 hours at 118°C - 125°C HPLC analysis indicated complete consumption of the methyl 4-hydroxybenzoate. Yield was 91.9% of theory. The potency of the product by HPLC versus a reference standard was 98.5%.

Example 12

Preparation of 6-methoxy-2-(4-methoxyphenyl) benzo[b]thiophene

A 100g portion of 3-methoxybenzenethiol and 39.1g of potassium hydroxide dissolved in 300mL of water were added to 750mL of denatured ethanol, and the flask was

put in a cooling bath. A total of 164g of α-bromo-1-methoxyacetophenone was then added in small portions, and the mixture was stirred for 10 minutes in the cooling bath after the addition was complete and then for 3 hours at ambient temperature. The solvent was then evaporated off in vacuum, and 200mL of water was added. The mixture was extracted with ethyl acetate, and the organic layer was washed twice with water, twice with aqueous sodium bicarbonate solution and twice with aqueous sodium chloride solution. The organic layer was then dried over magnesium sulfate, filtered and evaporated under vacuum to obtain 202g of crude a-(3-methoxyphenylthio)-4-methoxyacetophenone, which was recrystallized with hexane to obtain 158g of preferred product, mp. 53°C.

A 124g portion of the above intermediate was added in small portions to 930g of polyphosphoric acid at 85°C. The temperature rose to 95°C, during the addition, and the mixture was stirred at 90°C for 30 minutes after the addition was complete, and was then stirred an additional 45 minutes while it cooled without external heating. One liter of crushed ice was then added to the mixture, and the external ice bath was applied to control the temperature while the ice melted and diluted the acid. 500mL of additional water was added, and the light pink precipitate was filtered off and washed, first with water and then with methanol. The solids were dried under vacuum at 40°C to obtain 119g of crude 6-methoxy-2-(4-methoxyphenyl) benzo[b]thiophene. The crude product was slurried in hot methanol, filtered, and washed with cold methanol, and the solids were recrystallized from 4 liters of ethyl acetate, filtered, washed with hexane and

dried to obtain 68g of the desired intermediate product, m.p. 187°C - 190.5°C.

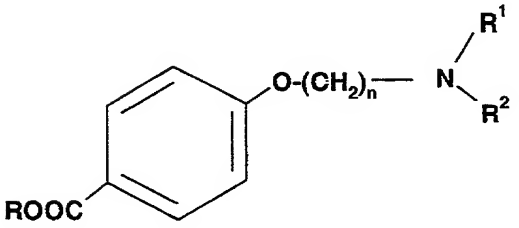
Example 13

Preparation of Raloxifene Hydrochloride [6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzyl]benzo[b]thiophene hydrochloride]

Under a nitrogen blanket, a mixture of 3g of 4-(2-piperidinoethoxy)benzoic acid, hydrochloride, 2 drops of dimethylformamide, 2.5mL of thionyl chloride and 40mL of chlorobenzene was heated at 70°C - 75°C for about 1 hour. The excess thionyl chloride and 15-20mL solvent were then distilled off. The remaining suspension was cooled to ambient temperature and to it were added 100mL of dichloromethane, 2.7g of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (preparation of which is described in Example 14) and 10g of aluminum chloride. After the solution was stirred for about 1 hour, 7.5mL of ethanethiol was added, and the mixture was stirred for an additional 45 minutes. Then 40mL of tetrahydrofuran was added, followed by 15mL of 20% hydrochloric acid, with an exotherm to reflux. 50mL of water and 25mL of saturated aqueous sodium chloride were added. The mixture was stirred and allowed to cool to ambient temperature. The precipitate was collected by filtration and washed successively with 30mL of water, 40mL of 25% aqueous tetrahydrofuran and 35mL of water. The solids were then dried at 40°C under vacuum to obtain 5.05g of product, which was identified by nuclear magnetic resonance as (6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-peridinoethoxy)benzyl]benzo[b]thiophene hydrochloride).

I claim:

1. A process for preparing a compound of formula I



I

wherein;

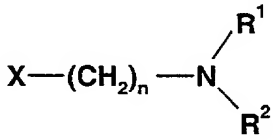
R is C_1-C_6 alkyl;

R^1 and R^2 each are independently C_1-C_4 alkyl, or combine together with the nitrogen atom to which R^1 and R^2 are attached, to form piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, or 1-hexamethyleneimino; and

n is 2 or 3;

or a pharmaceutically acceptable salt thereof, which comprises the step of:

reacting a haloalkyl amine of formula III

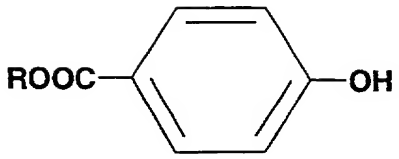


III

wherein;

X is a halogen; and

R^1, R^2, and n are as defined above, with a compound of formula IV



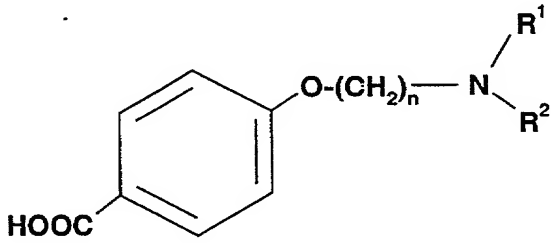
IV

wherein R is C_1-C_6 alkyl, in the presence of a hydrated inorganic base and an appropriate solvent.

2. The process according to Claim 1 further comprising the steps of:

a) extracting the reaction product of Claim 1 with an aqueous acid; and optionally

b) cleaving the ester of the reaction product from step a) to form an acid compound of formula Ia



Ia

3. A process according to Claim 1 wherein the hydrated inorganic base is selected from the group consisting of potassium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, calcium carbonate.

4. A process according to Claim 1 wherein the solvent is a C_1-C_6 alkyl acetate solvent selected from the

group consisting of amyl acetate, isopropyl acetate, isobutyl acetate and ethyl acetate.

5. A process according to Claim 1 wherein said C_1-C_6 alkyl acetate solvent is amyl acetate.

6. A process according to Claim 1 wherein said hydrated inorganic base is a carbonate or bicarbonate salt.

7. A process according to Claim 6 wherein said carbonate salt is potassium carbonate hydrated with 1-20% water.

8. A process according to Claim 7 wherein said hydrated potassium carbonate is achieved by adding bulk water.

9. A process according to Claim 7 wherein said hydrated potassium carbonate is achieved by water of hydration.

10. A process according to Claim 7 wherein said carbonate salt is potassium carbonate sesquihydrate.

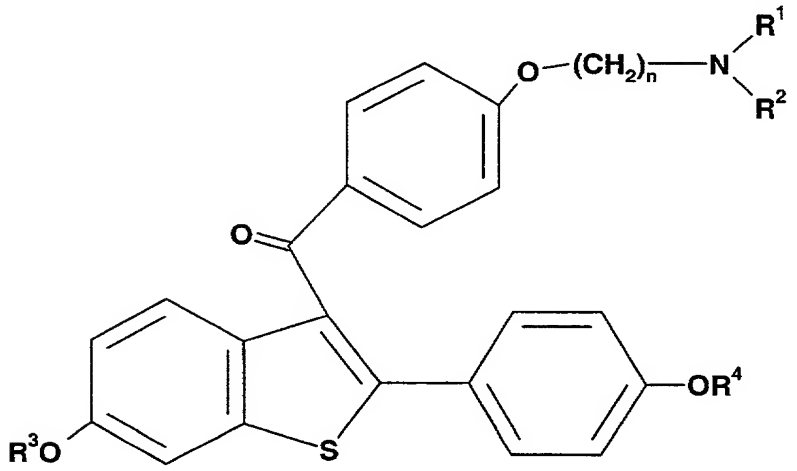
11. A process according to Claim 1 wherein R^1 and R^2 combine together with the nitrogen atom to which R^1 and R^2 are attached, to form piperidinyl; and

n is 2;

or a pharmaceutically acceptable salt thereof.

12. A process according to Claim 2 wherein said aqueous acid is hydrochloric acid.

13. A process according to Claim 2 for preparing compounds of formula II



II

wherein;

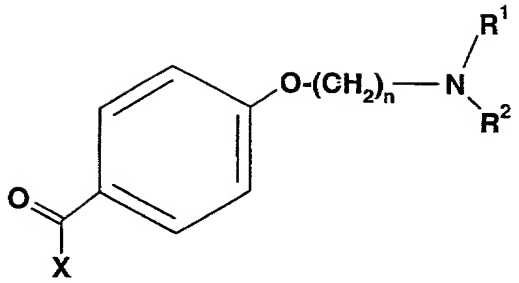
R^3 and R^4 are independently hydrogen or a hydroxy protecting group; and

R^1, R^2 and n are as defined above;

or a pharmaceutically acceptable salt thereof,

comprising the steps of:

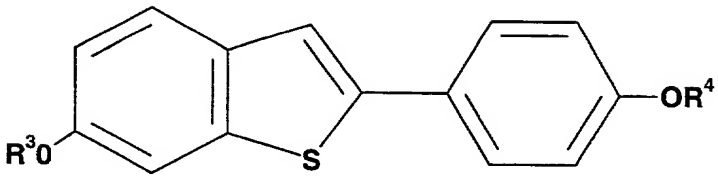
a) reacting a compound of formula I or Ia with an acyl halide forming agent to form a compound of formula V



V ;

wherein X is a halogen, and

b) reacting a compound of formula V with a compound of formula VI



VI

wherein R^3 and R^4 are as defined above, or a pharmaceutically acceptable salt thereof.

14. A process according to Claim 1 or 13 wherein; R^1 and R^2 combine with the nitrogen atom to which R^1 and R^2 are attached, to form a piperidinyl moiety, R^3 and R^4 each are hydrogen, and n is 2, or a pharmaceutically acceptable salt, solvate, or derivative thereof.

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(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **LUKE, Wayne, Douglas** [US/US]; 208 Jennings Street, West Lafayette, IN 47906 (US).

(74) Agents: **GINAH, Francis, O.** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

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WO 01/23369 A3

(54) Title: PROCESS FOR PREPARING BENZOIC ACIDS

(57) Abstract: An improved process for the preparation of 4[(2-piperidin-1-yl)ethoxy]benzoic acid derivatives, comprising reacting a haloalkyl amine of formula (III) with a compound of formula (IV) in the presence of a hydrated inorganic base in an appropriate solvent.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing

[ ] Declaration Submitted after Initial Filing

Attorney Docket Number	**X-11506**
First Named Inventor	**Wayne Douglas Luke**
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named Inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole Inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the Invention entitled:

PROCESS FOR PREPARING BENZOIC ACIDS

the specification of which
[ ] is attached hereto
OR
[X] was filed on (MM/DD/YYYY) 09/18/2000 as United States Application Number or PCT International Application Number PCT/US00/21974 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached YES	Certified Copy Attached NO
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/156,205	09/27/1999	[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box [+]

PTO/SB/01 (8-96) (MODIFIED)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Attorney Name	Reg. No.
Arvie J. Anderson	45,263
Lynn D. Apelgren	45,341
Robert A. Armitage	27,417
Brian P. Barrett	39,597
Michael T. Bates	34,121
Roger S. Benjamin	27,025
Gary M. Birch	48,881
William R. Boudreaux	35,796
Steven P. Caltrider	36,467
Paul R. Cantrell	36,470
John Cleveland	P50,697
Charles E. Cohen	34,565
Donald L. Corneglio	30,741
Gregory A. Cox	47,504
Paula K. Davis	47,517
Elizabeth A. Dawalt	44,646
John C. Demeter	30,167
Manisha A. Desai	43,585
Joanne Longo Feeney	35,134
Paul J. Gaylo	36,808
Francis O. Ginah	44,712
Janet A. Gongola	48,436
Amy E. Hamilton	33,894
James A. Hoffmann	P50,221
Frederick D. Hunter	26,915
Thomas E. Jackson	33,064
Soonhee Jang	44,802
Charles Joyner	30,466
Gerald P. Keleher	43,707

Attorney Name	Reg. No.
James J. Kelley	41,888
Paul J. Koivuniemi	31,533
Thomas LaGrandeur	P51,026
Robert E. Lee	27,919
Kirby Lee	47,744
James P. Leeds	35,241
Nelsen L. Lentz	38,537
Douglas K. Norman	33,267
Arleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
David M. Stemerick	40,187
Mark J. Stewart	43,936
Robert D. Titus	40,206
Robert C. Tucker	45,165
Tina M. Tucker	47,145
MaCharri Vorndran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

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☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	**ELI LILLY AND COMPANY**						
Address	**ATTN: Francis O. Ginah**						
Address	**LILLY CORPORATE CENTER/DC1104**						
City	**INDIANAPOLIS**	**State**	**INDIANA**	**ZIP**	**46285**		
Country		**Telephone**	**(317) 276-9477**	**Fax**	**(317) 276-3861**		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ **A Petition has been filed for this unsigned inventor**

Given Name	Wayne	Middle Name	Douglas	Family Name	Luke	Suffix e.g. Jr.	
Inventor's Signature	Wayne Douglas Luke TN					Date	3/5/2002
Residence: City	West Lafayette	State	IN	Country	US	Citizenship	US
Address	208 Jennings Street						
Post Office Address	SAME AS ABOVE						
City	West Lafayette	State	IN	Zip	47906	Country	US

☐ **Additional Inventors are being named on supplement sheet(s) attached hereto.**